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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,165	03/09/2001	Harald Sobek	5328	4735

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ROCHE MOLECULAR SYSTEMS INC
PATENT LAW DEPARTMENT
1145 ATLANTIC AVENUE
ALAMEDA, CA 94501

EXAMINER

ZARA, JANE J

ART UNIT

PAPER NUMBER

1635

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary

Application No.

09/803,165

Applicant(s)

SOBEK ET AL.

Examiner

Jane Zara

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 June 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 15 and 17-32 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15,17-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

DETAILED ACTION

This Office action is in response to the communication filed 6-14-04.

Claims 15, 17-34 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 15, 17-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reasons of record set forth in the Office action mailed 3-9-04.

Applicant's arguments filed 6-14-04 have been fully considered but they are not persuasive. Applicants argue that the instant invention, drawn to a thermostable mutant polymerase having at least 80% amino acid homology to SEQ id No: 34, whereby the tyrosine of the Y-GG/A motif between the N-terminal 3'-5' exonuclease domain and the C-terminal polymerase domain is substituted with another amino acid, is adequately described and the written description rejection is improper. Applicants assert that the instant specification provides both structural features of mutant polypeptides and a number of examples that are encompassed by the present claims, thereby satisfying the requirements set forth for adequate written description (e.g. that a representative number of species be described for the claimed genus). To support this assertion, Applicants argue that the structural basis for the catalytic activities of polymerases was

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generally understood as of the filing date of the instant application, that the art has recognized that B-type DNA polymerases exhibit a high degree of sequence homology, and furthermore that a list of polymerases from eight additional *Thermococcus* and *Prococcus* species that could also be modified according to the claimed invention has been provided. The instant specification teaches the mutagenesis of a single thermostable polymerase by methods well known in the art. Mutations were generated within a particular and previously characterized motif (Y-GG/A) in the polymerase molecule, and has been previously identified as being located between the exonuclease and polymerase domains of DNA polymerases (see e.g. Truniger et al. J. Mol. Biol. 286 at 57 and 58), and whose mutageneses in other polymerases have yielded mutants with altered polymerase and/or exonuclease activities (*Id.* at Table 1 on p. 61). Contrary to Applicants' assertions, the mutagenesis of a single polymerase is not representative of the mutagenesis of any polymerase sharing 80% or greater homology with that polypeptide sequence. Applicants are correct that sequence homologies have been provided in the instant disclosure for various polymerases. But, contrary to Applicants' assertions, the listing in the specification of known polymerases that share homology with the polymerase of the instantly claimed invention (SEQ ID NO: 34) does not provide adequate description of thermostable mutant polymerases bearing the claimed characteristics (e.g. thermostable, and able to amplify DNA as described in claim 34). No correlation between sequence homology and higher order polymerase structure has been taught in the instant disclosure, whereby mutations generated in the Y-GG/A motif render the mutant polymerases thermostable. No concise structural features of this

broad genus have been taught in the instant disclosure, whereby sequences with 80% or greater homology with SEQ ID NO: 34 are rendered thermostable polymerases and are distinguished from members outside the claimed genus. The description of mutagenesis of a single member of the genus is not representative of the vast array of sequences claimed. No relationship between the sequences claimed, their loop conformations, domain conformations and phenotypes observed following mutagenesis, that would distinguish members of the genus from those outside the genus, has been provided in the instant disclosure. The general knowledge and skill in the art teach that a fragile conformation exists in this (solvent accessible) loop bearing the Y-GG/A motif, and that this loop links the two catalytic domains of DNA polymerases. It is the fragile conformation of this loop that is believed to contribute to "diverse phenotypes seen after mutations in the Y-GG/A motif" (See Bohlke et al at 3916, last paragraph). No concise structural characteristics have been provided that distinguish members of this genus from others. Applicants seek on the one hand to distinguish their invention from previous polymerases bearing these mutations in the Y-GG/A motif by emphasizing the differences observed upon mutagenesis of Sso or bacteriophage 29 DNA polymerases (e.g. lacking PCR activity, mutations resulted in loss of thermostable polymerase activity), and on the other hand seek to generalize structural relationships between all polymerases sharing 80% homology or greater. But no common structural relationships shared by the claimed genus - yet absent in other polymerases - have been firmly established or described.

Applicants also argue that the structural basis for catalytic activities of polymerases was generally understood at time of filing and that crystal structures of a number of polymerases have been solved. Contrary to Applicants assertions, the structural basis for catalytic activities of polymerases provided in the specification does not distinguish thermostable, mutagenized polymerases, based on percentage of homology, from those outside of the claimed genus. The general structures disclosed appear to be applicable to a broader array of polymerases (see page first full paragraph of the specification). It is unclear why Applicants included homologs of 80% or greater in this genus. As for crystal structure information, Bohlke et al (published after September of 2000 - well after the claimed priority date of the instant application, 3-11-00) teach that two crystal structures were available for B-type DNA polymerases (see Bohlke, p. 3910, last full paragraph). Attempts were made in this work to correlate Y-GG/A mutations, the resulting changes in polymerase and exonuclease activity (i.e. by Km), and higher order structure. But, as this publication teaches, no concise higher order structural attributes can be generalized using the existing body of data available: "The tyrosine... in our structural model... is almost completely buried. Phe, Trp or His could occupy the same position, whereas it is less clear if the environment would also accommodate the comparatively polar Asn and Ser residues. If not, this could lead to a different conformation of the loop taking part in the generation of the described phenotypes... Final evidence for the exact role of the tyrosine in the flexible loop will be accessible only with the help of a binary crystal structure from the relevant DNA polymerase with duplex DNA bound to its polymerase active site." (see last two

paragraphs on p. 3916). One of skill in the art would reasonably conclude that the disclosure and the art fail to provide a correlation between sequence homology and higher order structure so that concise features are adequately described for the claimed genus. One of skill in the art would also reasonably conclude that the disclosure fails to provide a representative number of species to describe the broad genus claimed (one polymerase sequence with various mutations does not provide the necessary representation). Thus, Applicants were not in possession of the claimed genus.

Allowable Subject Matter

SEQ ID NO: 34 comprising a single amino acid substitution of tyrosine of the Y-GG/A amino acid motif appears free of the prior art searched and of record.

Claim 19 is objected to for being dependent upon a rejected claim.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

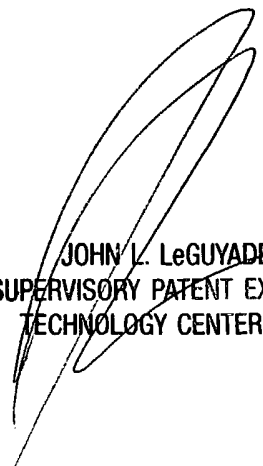
A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765**. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ
9-2-04



JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600